Myeloablative conditioning regimens may cause life threatening transplant related toxicities in patients with primary immunodeficiency disorders (PID), particularly in patients with co-morbid conditions. We previously reported the outcomes of a phase I study using nonmyeloablative conditioning in 14 high-risk patients and demonstrated low transplant related mortality (TRM; 3-year, 23%); however there was a high incidence of chronic GVHD (1-year 47%). We reasoned that the incidence of GVHD could be reduced if marrow was used instead of PBSC; however, previous experience showed marrow to be associated with a higher risk for rejection. Therefore our standard nonmyeloablative regimen of 90 mg/m^2 fludarabine and 2 Gy total body irradiation (TBI) was somewhat intensified to include either Campath 1-H, or, for patients with infections for whom Campath 1-H was contraindicated, an additional 2 Gy TBI.

Sixteen patients with PID and significant underlying infections and/or other co-morbidities were given HLA-matched related (n = 7) or unrelated (n = 9) marrow grafts following nonmyeloablative conditioning modified with either Campath 1-H (n = 3) or 4 Gy TBI (n = 13). All patients were given postgrafting immunosuppression with MMF and CSP. Of the 15 patients evaluable for engraftment, mixed (50-95%; n = 8) or full (>95%; n = 6) donor CD3 + T-cell chimerism was established in 14 patients. Two patients required a 2nd myeloablative HCT due to graft rejection or loss of the granulocyte and NK cell components of the graft despite stable mixed T-cell chimerism. The cumulative incidence of extensive chronic GVHD at 1 year was 29%. With a median follow-up of 19 (range, 3 – 36) months the 1-year overall survival and TRM were 87% and 14%, respectively. One patient with disseminated CMV and adenovirus before HCT died from these infections at day +1 and one patient with pre existing renal failure died at day +222 from complications of renal failure. Five patients were not evaluable for disease response due to less than 100 days of follow-up (n = 2), 2nd HCT (n = 2), or death prior to day 100 following HCT (n = 1). Eleven patients had improvement in or correction of their underlying immunodeficiency. Although preliminary, these results indicate that outcome can be improved for high-risk patients with PID using a modified nonmyeloablative conditioning regimen and marrow grafts, resulting in reduction of chronic GVHD, stable donor engraftment, low TRM, and correction of underlying disease processes.

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CLINICAL OUTCOMES OF PEDIATRIC PATIENTS REQUIRING INTENSIVE CARDIOPULMONARY SUPPORT DURING HSCT

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This is a multi-center, case controlled, retrospective study of the short-term and 1-year outcomes of children who received intensive cardiopulmonary (CP) support during the HSCT admission at seven tertiary care facilities. Intensive CP support was defined as the need for continuous positive pressure ventilation, dopamine greater than or equal to10 mcg/kg/min, or the use of other cardiotropic drug. We compared the outcomes of 94 patients who required intensive CP care to 282 patients hospitalized during the same period who did not receive intensive CP support. Demographic and transplant data are summarized below. Respiratory failure was the most common indication for CP care (75.5%) followed by sepsis (10.6%), neurologic event (4.3%), cardiac compromise (2.1%), multi-system organ failure (MSOF) (2.1%), and other causes (5.4%). Acute GVHD was present in 21% of patients and macroscopic bleeding in 26% at the onset of CP support. 46% of patients had a pediatric logistic organ dysfunction score of at least 1 in two organ systems at the start of CP support. 44% of patients needed noninvasive ventilation (median duration 2 days). Of this 44%, 66% later required invasive ventilation, 22% successfully discontinued support, and 12% died. 82% of CP patients received invasive ventilation (median duration 8 days) and 38% died prior to discharge. 50% of patients needed cardiac medications. The median duration CP support was 18.6 days. 44.7% of patients died prior to discharge from CP support, 52.1% transitioned to non-intensive CP care, and 3.2% returned to the HSCT unit for palliation. MSOF was the most common cause of death (51%). 39% of patients who survived initial CP support needed additional intensive CP care and 58% of these patients died prior to discharge. Survival to hospital discharge was 37.2% in the CP group and 98.9% in the non-CP group. OS at 1-year was 32% and 78% in the CP and non-CP groups. The 1-year overall survival (86% vs. 79%) and disease-free survival (69% vs 72%) of CP and non-CP patients who survived to hospital discharge were not significantly different. The 1-year relapse rate, incidence of GVHD, mean FEV_1, shortening fraction, and creatinine were not significantly different between the two groups. The survival rate of pediatric patients requiring intensive CP support has improved, but remains suboptimal. No significant difference existed in 1-year organ function or survival among patients who did or did not receive intensive CP support.

Demographic and Transplant Data

	Case, n = 94	Control, n = 282
Age median (months)	67	97
Diagnosis (%)		
ALL CR1/CR2	5.3/12.8	8.9/17
AML CR1/CR2	7.4/5.3	11/8.5
Metabolic Disease	12.8	8.5
Immunodeficiency	1.7	4.3
Nonmalignant Hematologic Disease	10.6	9.5
Solid Tumor	13.8	17.7
Myelodysplasia	2.1	1.8
HLH	6.4	0.7
Lymphoma	4	5
Osteopetrosis	3.2	0.4
JMML	2.1	0.7
Other	5.3	6.5
Autolgous HSCT	18.1	18.4
Allogeneic HSCT	81.9	81.5
Donor Source (%)		
6/6 Related Donor	14.3	35.8
< 6/6 Related Donor	9.1	6.6
6/6 Unrelated Donor	26	26.2
<6/6 Unrelated Donor	50.6	31.4

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TARGETED BIOLOGICAL THERAPY FOR HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS IN A MURINE DISEASE MODEL

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Hemophagocytic lymphohistiocytosis (HLH) is a rare and usually fatal hyperinflammatory disorder associated with genetic defects of CD8 + T cell and NK cell cytotoxic function. Jordan, et al (Blood 2004;104(3):735-43) previously showed that perforin-deficient (prf-/-) mice infected with lymphocytic choriomeningitis virus (LCMV) develop a disorder which is essentially identical to human HLH. In this animal model of HLH, ineffective cytotoxic CD8 + T cells fail to down-modulate stimulatory signals from antigen presenting cells. Exaggerated T cell responses are responsible for massive cytokine production, especially interferon-gamma (IFN-γ), which drives systemic macrophage activation and results in HLH-like disease pathology. Thus, at least three critical events occur in the pathogenesis of HLH: 1) abnormal increase in antigen presentation, 2) abnormal increase in CD8 + T cell activation and cytokine secretion, and 3) pathological macrophage activation.

Survival with current standard HLH therapy, consisting of cytotoxic chemotherapy (etoposide) and nonspecific immunosuppression (dexamethasone), is approximately 75% at 8 weeks. Ongoing studies using our murine model of HLH indicate that etoposide acts primarily by deleting activated IFNγ-producing T cells. While beneficial in